REMARKS

Prior to the present amendment, Claims 1, 2, 11, 12, 34 and 36 were pending. By the present amendment, Claims 1, 2 and 34 are cancelled. Accordingly, Claim 11, 12, and 36 are currently pending.

35 U.S.C. 103 REJECTION

Claims 1, 2, 11, 12, 34, and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 02/36144 (hereinafter "*Arnold*") in view of U.S. Patent Publication No. 2003/0229088 (hereinafter "*Gil*") citing to Burke et al., "Preclinical Evaluation of Brimonidine," Survey of Ophthalmology, 41(1):S9-S18 (1996) (hereinafter "*Burke*") as evidenced by Wymenga et al., "Management of Hot Flushes in Breast Cancer Patients," *Acta Oncologia 41(3)*:269-275(2002) (hereinafter "*Wymenga*") and EP 1069124 (hereinafter "*Ito*").

According to the examiner, the primary reference *Arnold* discloses a medicament useful for treating side effects of ovarectomy or symptoms associated with menopause, wherein such symptoms include vasomotor symptoms, e.g., hot flushes. The medicament includes one or more GnRH analogue compound. Optionally, other compounds can be included, e.g., α-adrenergic agonists. (Office Action page 3, 1st full paragraph.)

The examiner concedes that *Arnold* does **not** disclose the use of brimonidine or brimonidine tartrate as the α-adrenergic agonist, does **not** disclose topical administration of the medicament locally to the site of the facial flushing, and does not disclose the concomitant use of an additional agent as provided in Claims 11 and 12. (Office Action page 3, 2nd full paragraph.)

In an attempt to remedy the deficiencies in *Arnold*, the examiner relies upon *Gil* for allegedly disclosing known α-adrenergic agonists, including clonidine, brimonidine, tizanidine, etc., and salts thereof, in dermatologically acceptable formulations, e.g., a dermal patch, topical drops, creams, gels and ointments. According to the examiner, it would have been obvious to employ brimonidine, or a salt thereof, in the medicament disclosed by *Arnold* because *Gil* discloses that brimonidine is "one of a finite number of α-adrenergic agonists known in the art at the time of the invention to predictably function as an agonist of α-adreno-receptors." (Office Action page 3, last paragraph.)

The examiner relies upon *Burke* for disclosing that brimonidine has at least 2-fold to 50-fold greater selectivity for the α-2-adreno-receptor vis-à-vis clonidine. The examiner relies upon *Wymenga* for disclosing the administration of vitamin E for treating patients experiencing hot flushes. Finally, the examiner relies upon *Ito* for disclosing that compounds, which are not related to brimonidine, for treating inflammatory diseases such as vasomotor disturbances, including hot flushes, may be administered topically to the skin by way of creams, gels, pastes, ointments, etc. (Office Action paragraph bridging pages 4 and 5.)

Applicant respectfully asserts that considering the references as a whole, a skilled artisan would not have been lead to treat hot flushes topically with α-adreno-agonists. As conceded by the examiner, Arnold does **not** disclose topical administration of their composition to treat hot flushes. The examiner relies on *Gil* for teaching topical administration of α-adreno-agonists such as brimonidine. However, *Gil* relates exclusively to the treatment of pain. Since the etiology of pain and hot flushes are not related, the topical treatment of pain with α-adreno-agonists would not have suggested the topical treatment of hot flushes with α-adreno-agonists.

The examiner also attempts to rely on *Ito* for the disclosure of treating hot flushes with a composition which may be topically administered. However, the examiner seems to misinterpret *Ito*. The only embodiment for which *Ito* teaches topical administration is "when treating inflammatory conditions of the skin..." (paragraph [0027]). However, *Ito* does not state that hot flushes are inflammatory conditions of the skin. Instead, hot flushes have a hormonal etiology. Thus, *Ito* does not teach topical treatment of hot flushes.

Moreover, the *Ito* composition is completely unrelated to α-adreno-agonists. The mechanism of action of the *Ito* composition is by agonizing ORL-1 receptors. Since the mechanism of action of the present composition and the *Ito* composition are not related, a skilled artisan would not have been taught to treat hot flushes topically.

It should also be noted that the only α-adrenero-receptor agonists mentioned in *Arnold* are phenylpropanolamine and phenylephrine. Phenylpropanol-amine is used in a veterinary preparation to control urinary incontinence in dogs. Phenylephrine is used primarily as a decongestant. Thus, *Arnold* does not even hint at treating hot flushes with α-adrenero-receptor agonists.

Nevertheless, in order to expedite prosecution, independent Claim 1, and dependent Claims 2 and 34, have been cancelled. Independent Claim 36 has been amended to further define the topically-administered-composition by which to treat facial flushing as comprising an effective amount of a single component that acts locally to reduce cutaneous facial flushing, wherein the component consists of brimonidine and/or brimonidine tartrate. That is, only one component in the composition acts to reduce the flushing. (Support for this amendment can be found throughout the specification, including page 6, lines 4-7 and 27-30.)

In contrast, the ingredient in the medicament of *Arnold* which treats flushing is a **GnRH analogue**. As the examiner correctly pointed out, *Arnold* discloses that α-adrenergic receptor agonists are simply optional ingredients (along with six other broad categories of actives) in its medicaments. See page 12, second full paragraph of *Arnold*. Thus, *Arnold* does not teach that α-adrenergic receptor agonists treat flushing.

Amended Claim 36 excludes a GnRH analogue as an active ingredient. Instead, Claim 36 requires brimonidine and/or brimonidine tartrate as the active component in the composition.

In order for a prima facie obviousness rejection to be made, all the claim limitations must be found in the cited prior art. None of the references teach topical treatment of cutaneous facial flushing with the single active ingredient of brimonidine and/or brimonidine tartrate. Accordingly, applicant respectfully request withdrawal of the obvious rejection.

Applicant respectfully submits that the application is now in proper form for allowance, which action is earnestly solicited. If resolution of any remaining issue is required prior to allowance of the application, it is respectfully requested that the examiner contact applicant's attorney at the telephone number provided below.

Respectfully submitted,

/susan a. sipos/
Susan A. Sipos
Registration No.: 43,128
Attorney for Applicant

HOFFMANN & BARON, LLP
6900 Jericho Turnpike
Syosset, New York 11791
Tel. (516) 822-3550
Fax. (516) 822-3582